(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
18 November 2004 (18.11.2004)

PCT

(10) International Publication Number
WO 2004/099183 A1

(51) International Patent Classification[7]: C07D 401/12

(21) International Application Number:
PCT/IN2003/000177

(22) International Filing Date: 6 May 2003 (06.05.2003)

(25) Filing Language: English

(26) Publication Language: English

(71) Applicant *(for all designated States except US)*: **HETERO DRUGS LIMITED** [IN/IN]; Hetero House, 8-3-166/7/1, Erragadda, Hyderabad 500 018, Andhra Pradesh (IN).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **PARTHASARADHI REDDY, Bandi** [IN/IN]; Hetero House, 8-3-166/7/1, Erragadda, Hyderabad 500 018, Andhra Pradesh (IN). **RATHNAKAR REDDY, Kura** [IN/IN]; Hetero Drugs Limited (R & D), Plot No. B-80 & 81, A.P.I.E., Balanagar, Hyderabad 500 018, Andhra Pradesh (IN). **RAJI REDDY, Rapolu** [IN/IN]; Hetero Drugs Limited (R & D), Plot No. B-80 & 81, A.P.I.E., Balanagar, Hyderabad 500 018, Andhra Pradesh (IN). **MURALIDHARA REDDY, Dasari** [IN/IN]; Hetero Drugs Limited (R & D), Plot No. B-80 & 81, A.P.I.E., Balanagar, Hyderabad 500 018, Andhra Pradesh (IN). **SUBASH CHANDER REDDY, Kesireddy** [IN/IN]; Hetero Drugs Limited (R & D), Plot No. B-80 & 81, A.P.I.E., Balanagar, Hyderabad 500 018, Andhra Pradesh (IN).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

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— *of inventorship (Rule 4.17(iv)) for US only*

Published:

— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: NOVEL POLYMORPHS OF PANTOPRAZOLE SODIUM

(57) Abstract: The present invention relates to novel polymorphs of pantoprazole sodium, to processes for their preparation and to pharmaceutical compositions containing them.

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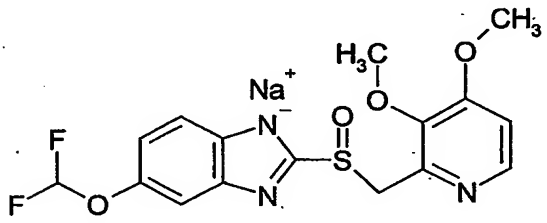
NOVEL POLYMORPHS OF PANTOPRAZOLE SODIUM

FIELD OF THE INVENTION

The present invention relates to novel polymorphs of pantoprazole sodium, to processes for their preparation and to pharmaceutical compositions containing them.

BACKGROUND OF THE INVENTION

Pantoprazole sodium, chemically 5-(Difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt, is represented by the following structure:



Pantoprazole sodium is an antiulcerative, which is disclosed and claimed in US 4,758,579. A crystalline form of pantoprazole sodium is mentioned in Analytical Profiles of Drug Substances and Excipients - volueme 29, year 2002, page no. 213-259.

We have discovered two stable novel crystalline forms and these forms are at least as stable as the reported form. The novel crystalline forms are stable over the time. We have also discovered a sufficiently stable amorphous form of pantoprazole sodium. So, these forms can be utilized to prepare stable pharmaceutical dosage forms.

The object of the present invention is to provide stable polymorphs of pantoprazole sodium, processes for preparing these forms and pharmaceutical compositions containing them.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, there is provided a novel crystalline form of pantoprazole sodium, designated as form I, characterized by an x-ray powder diffraction spectrum having peaks expressed as 2θ at about 5.3, 13.1, 13.5, 14.8, 20.7, 21.8 and 25.6 degrees. Figure 1 shows typical form I x-ray powder diffraction spectrum.

In accordance with the present invention, a process is provided for preparation of pantoprazole sodium form I. Pantoprazole sodium form I is prepared by dissolving pantoprazole sodium in a suitable solvent and isolating pantoprazole sodium form I from the solution by adding an anti-solvent. Pantoprazole sodium in any crystalline or amorphous form may be used in the process. The quantity of the anti-solvent should be at least sufficient to precipitate pantoprazole sodium from the solution.

In accordance with the present invention, an another process is provided for preparation of pantoprazole sodium form I. Pantoprazole sodium form I is prepared by dissolving pantoprazole in a suitable solvent, adding sodium hydroxide to the solution and then isolating pantoprazole sodium form I from the solution by adding an anti-solvent. The quantity of sodium hydroxide to pantoprazole is not limiting, but 0.5 to 2.0 moles of sodium hydroxide per mole of pantoprazole is preferable. The quantity of the anti-solvent should be at least sufficient to precipitate pantoprazole sodium from the solution.

In accordance with the present invention, there is provided a novel crystalline form of pantoprazole sodium, designated as form II, characterized by an x-ray powder diffraction spectrum having peaks expressed as 2θ at about 5.4, 8.7, 14.0, 15.1, 15.4, 16.2, 18.3, 18.9, 19.6, 19.9, 20.8, 21.3, 22.1, 23.1, 25.6, 28.2 and 28.6 degrees. Figure 2 shows typical form II x-ray powder diffraction spectrum.

In accordance with the present invention, a process is provided for preparation of pantoprazole sodium form II. Pantoprazole sodium form II prepared by dissolving pantoprazole sodium in acetonitrile and isolating pantoprazole sodium form II from the solution by adding an anti-solvent. Pantoprazole sodium in any crystalline or amorphous form may be used in the

process. The quantity of the anti-solvent should be at least sufficient to precipitate pantoprazole sodium from the solution.

In accordance with the present invention, an another process is provided for preparation of pantoprazole sodium form II. Pantoprazole sodium form II is prepared by dissolving pantoprazole in acetonitrile, adding sodium hydroxide and isolating pantoprazole sodium form II from the solution by adding an anti-solvent. The quantity of sodium hydroxide to pantoprazole is not limiting, but 0.5 to 2.0 moles of sodium hydroxide per mole of pantoprazole is preferable. The quantity of the anti-solvent should be at least sufficient to precipitate pantoprazole sodium from the solution.

In accordance with the present invention, there is provided a novel amorphous form of pantoprazole sodium, designated as amorphous pantoprazole sodium, characterized by having broad x-ray diffraction spectrum as in figure 3.

In accordance with the present invention, a process is provided for preparation of amorphous pantoprazole sodium. Amorphous pantoprazole sodium is prepared by dissolving pantoprazole sodium in an alcohol or a mixture of alcohols and removing the solvents from the solution. Pantoprazole sodium in any crystalline or amorphous form may be used in the process. The alcohol is selected from the group consisting of methanol, ethanol and isopropyl alcohol. The solvent may be removed from the solution by vacuum drying or spray drying.

The 'suitable solvents' used in the above processes are methanol, ethanol, isopropyl alcohol and acetone; and a mixture thereof.

Preferable 'anti-solvent' is diisopropyl ether or toluene; or a mixture thereof.

In accordance with the present invention, there is provided a pharmaceutical composition comprising pantoprazole sodium form I and a pharmaceutically acceptable carrier or diluent.

In accordance with the present invention, there is provided a pharmaceutical composition comprising pantoprazole sodium form II and a pharmaceutically acceptable carrier or diluent.

In accordance with the present invention, there is provided a pharmaceutical composition comprising amorphous pantoprazole sodium and a pharmaceutically acceptable carrier or diluent.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a x-ray powder diffraction spectrum of pantoprazole sodium form I.

Figure 2 is a x-ray powder diffraction spectrum of pantoprazole sodium form II.

Figure 3 is a x-ray powder diffraction spectrum of amorphous pantoprazole sodium.

x-Ray powder diffraction spectrum was measured on a Bruker axs D8 advance x-ray powder diffractometer having a copper-Kα radiation.

The invention will now be further described by the following examples, which are illustrative rather than limiting. Pantoprazole and pantoprazole sodium used in the following examples are obtained from the previously known methods.

Example 1

Pantoprazole sodium (5.0 gm) is dissolved in methanol (15 ml) at 30°C and then diisopropyl ether (250 ml) is added. The contents are stirred for 24 hours at 25°C to 30°C and filtered to give 4.8 gm of pantoprazole sodium form I.

Example 2

Pantoprazole (10.0 gm) is dissolved in methanol (30 ml), sodium hydroxide (1.1 gm) is added at 25°C and stirred for 2 hours at 25°C to 30°C. Then diisopropyl ether (250 ml) is added to the solution and stirred for 1 hour at 25°C to 28°C. The separated solid is filtered to give 9.0 gm of pantoprazole sodium form I.

Example 3

Pantoprazole sodium (10.0 gm) is dissolved in acetonitrile (50 ml) at 30°C and then diisopropyl ether (300 ml) is added. The contents are stirred for 6 hours at 25°C to 30°C and filtered to give 4.5 gm of pantoprazole sodium form II.

Example 4

Pantoprazole (10.0 gm) is dissolved in acetonitrile (50 ml), sodium hydroxide (1.1 gm) is added slowly at 25°C to the clear solution. The contents are stirred for 3 hours at 25°C to 30°C. Then diisopropyl ether (300 ml) is added to the solution and stirred for 2 hours at 25°C to 30°C. The separated solid is filtered to give 9.1 gm of pantoprazole sodium form II.

Example 5

Pantoprazole sodium (5.0 gm) is mixed with toluene (100 ml), heated to 70°C and then acetonitirile (50 ml) is added to form a clear solution. The solution is cooled to 30°C, stirred for 20 hours at 25°C to 30°C and the separated solid is filtered to give 4.3 gm of pantoprazole sodium form II.

Example 6

Example 3 is repeated using pantoprazole sodium form I instead of pantoprazole sodium. The yield of pantoprazole sodium form II is 4.1 gm.

Example 7

Example 1 is repeated using pantoprazole sodium form II instead of pantoprazole sodium. The yield of pantoprazole sodium form I is 4.6 gm.

Example 8

Pantoprazole sodium (5.0 gm) is dissolved in methanol (50 ml) at 25°C. The solution is subjected to vacuum drying at about 50°C for 7 hours to give amorphous pantoprazole sodium in near quantitative yield.

Example 9

Example 8 is repeated by subjecting the solution to spray drying instead of vacuum drying to give amorphous pantoprazole sodium.

We claim:

1. A crystalline pantoprazole sodium form I, characterized by an x-ray powder diffraction spectrum having peaks expressed as 2θ at about 5.3, 13.1, 13.5, 14.8, 20.7, 21.8 and 25.6 degrees.
2. A crystalline pantoprazole sodium form I as defined in claim 1, further characterized by an x-ray powder diffraction spectrum as in figure 1.
3. A process for preparation of pantoprazole sodium form I as defined in claim 1, which comprises the steps of:

a) dissolving pantoprazole sodium in a suitable solvent; and
b) isolating pantoprazole sodium form I from the solution formed in (a) by adding anti-solvent;

wherein the suitable solvents are methanol, ethanol, isopropyl alcohol and acetone and a mixture thereof.

4. A process according to claim 3, wherein the suitable solvent is methanol or ethanol.
5. A process according to claim 3, wherein the anti-solvent is diisopropyl ether or toluene.
6. An another process for preparation pantoprazole sodium form I as defined in claim 1, which comprises the steps of:

a) dissolving pantoprazole in a suitable solvent;
b) adding sodium hydroxide; and
c) isolating pantoprazole sodium form I from the solution formed in (b) by adding an anti-solvent;

wherein the suitable solvents are methanol, ethanol, isopropyl alcohol and acetone and a mixture thereof.

7. A process according to claim 6, wherein the suitable solvent is methanol or ethanol.
8. A process according to claim 6, wherein the anti-solvent is diisopropyl ether or toluene.
9. A crystalline pantoprazole sodium form II, characterized by an x-ray powder diffraction spectrum having peaks expressed as 2θ at about 5.4, 8.7, 14.0, 15.1, 15.4, 16.2, 18.3, 18.9, 19.6, 19.9, 20.8, 21.3, 22.1, 23.1, 25.6, 28.2 and 28.6 degrees.

10. A crystalline pantoprazole sodium form II as defined in claim 9, further characterized by an x-ray powder diffraction spectrum as in figure 2.
11. A process for preparation of pantoprazole sodium form II as defined in claim 9, which comprises the steps of:

a) dissolving pantoprazole sodium in acetonitrile; and
b) isolating pantoprazole sodium form II from the solution formed in (a) by adding an anti-solvent.

12. A process according to claim 11, wherein the anti-solvent is diisopropyl ether.
13. A process according to claim 11, wherein the anti-solvent is toluene.
14. An another process for preparation pantoprazole sodium form II as defined in claim 9, which comprises the steps of:

a) dissolving pantoprazole in acetonitrile;
b) adding sodium hydroxide; and
c) isolating pantoprazole sodium form II from the solution formed in (b) by adding an anti-solvent.

15. A process according to claim 14, wherein the anti-solvent is diisopropyl ether.
16. A process according to claim 14, wherein the anti-solvent is toluene.
17. Amorphous pantoprazole sodium characterized by an x-ray powder diffraction spectrum as in figure 3.
18. A process for preparation of amorphous pantoprazole sodium of claim 17, which comprises the steps of:

a) dissolving pantoprazole sodium in an alcohol or a mixture of alcohols;
b) removing the solvents from the solution formed in (a) either by vacuum drying or by spray drying;

wherein the alcohol is selected from the group consisting of methanol, ethanol and isopropyl alcohol.

19. A process according to claim 18, wherein the solvent is removed by vacuum drying.
20. A process according to claim 18, wherein the solvent is removed by spray drying.
21. A pharmaceutical composition comprising pantoprazole sodium form I of claim 1 and a pharmaceutically acceptable carrier or diluent.

22. A pharmaceutical composition comprising pantoprazole sodium form II of claim 9 and a pharmaceutically acceptable carrier or diluent.
23. A pharmaceutical composition comprising amorphous pantoprazole sodium of claim 17 and a pharmaceutically acceptable carrier or diluent.

fig. 1/3

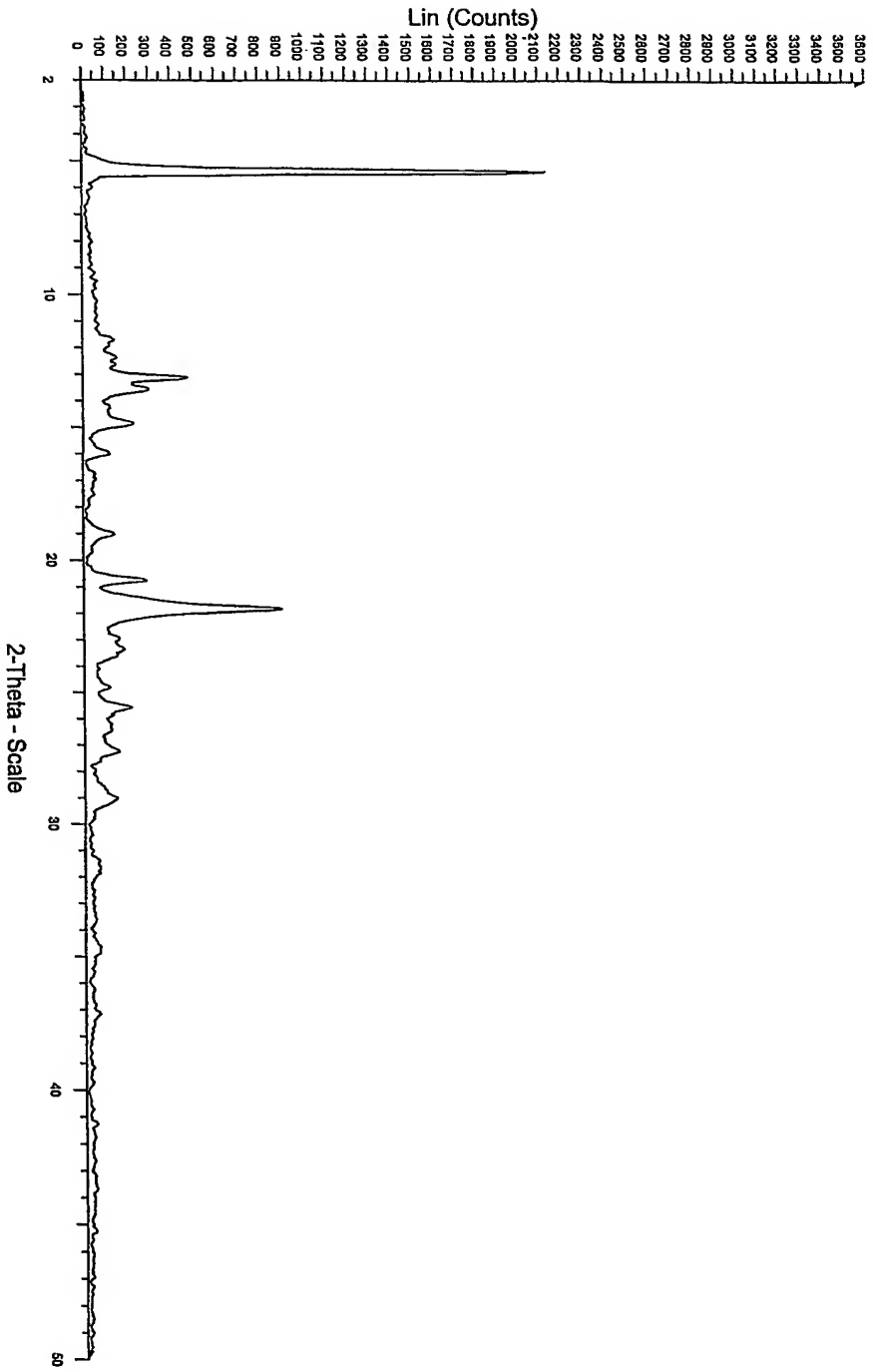

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fig. 2/3

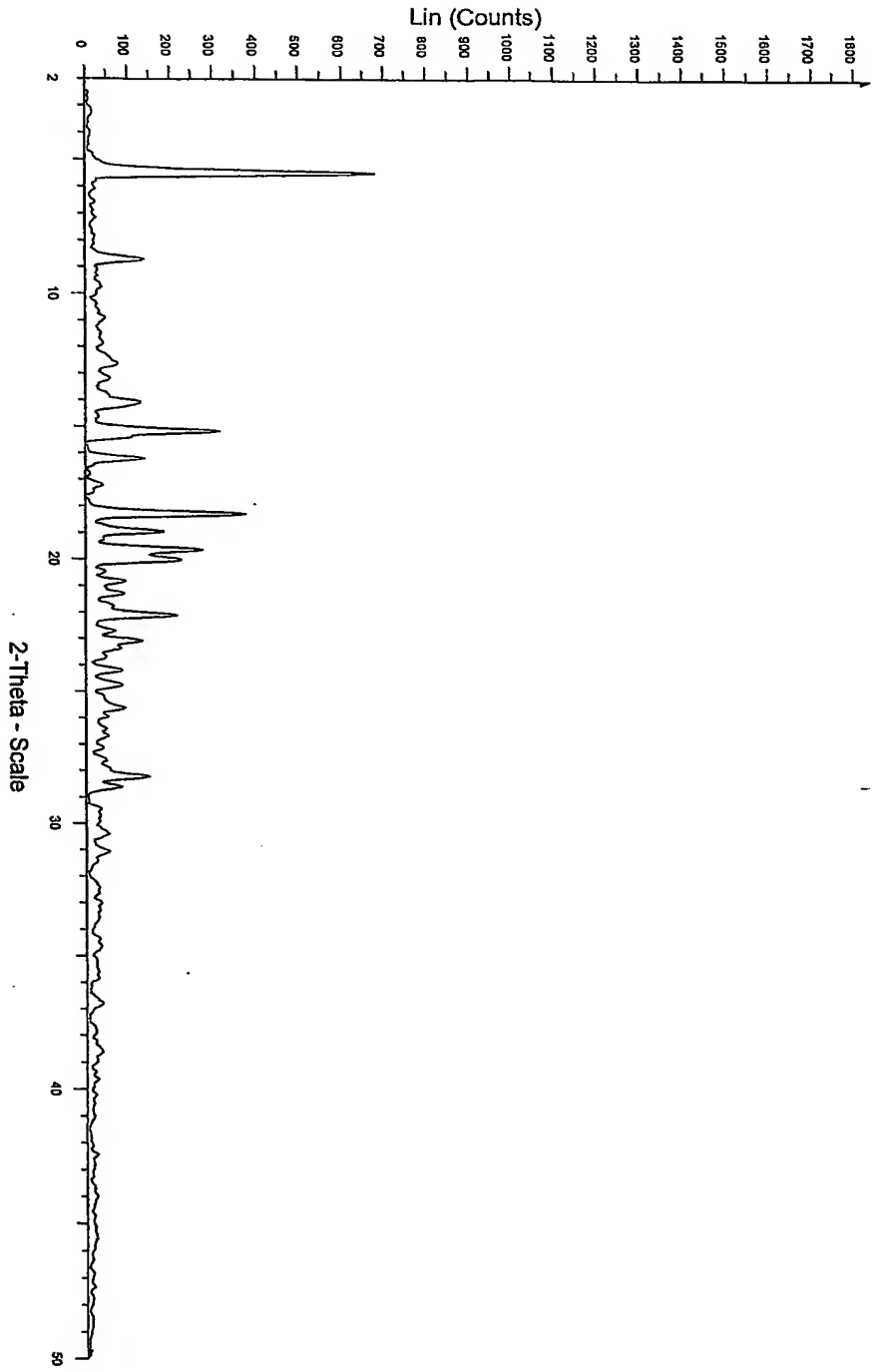
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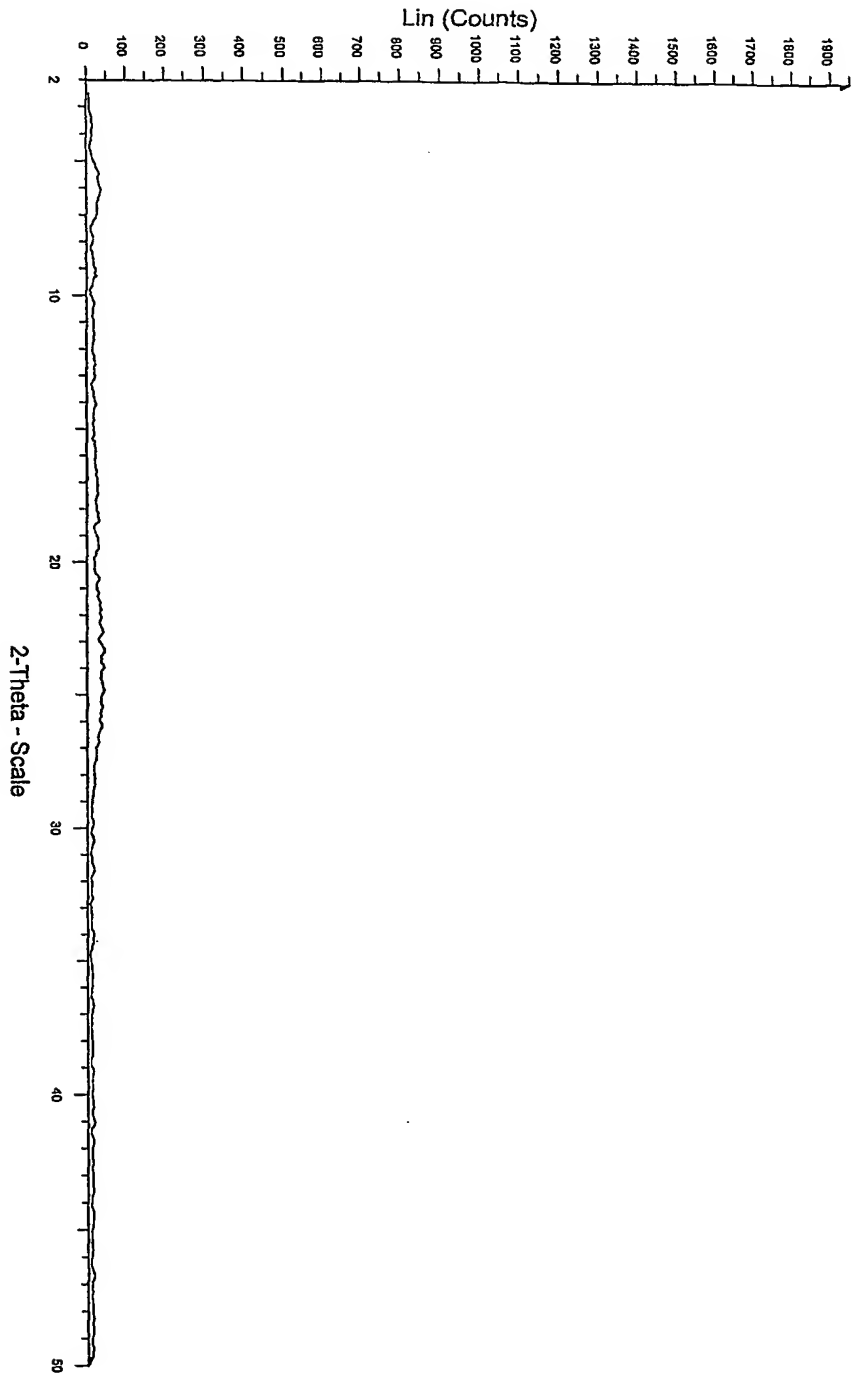
fig. 3/3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INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN 03/00177-0

CLASSIFICATION OF SUBJECT MATTER

IPC[7]: C07D 401/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[7]: C07D 401/12

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPOQUE: WPI, EPODOC, STN (Karlsruhe) CAS: REGISTRY and CA databases

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
D,X	A. A. BADWAN et al., "PANTOPRAZOLE SODIUM", Analytical Profiles of Drug Substances and Excipients, 29, 2002, pages 213-259 *the whole document, especially table 1.*	1-8,21
X	WO 02/41919 A1 (BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH) 30 May 2003 (30.05.03) *example 2,3.*	17-20,23

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
„A" document defining the general state of the art which is not considered to be of particular relevance
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Date of the actual completion of the international search	Date of mailing of the international search report
14 January 2004 (14.01.2004)	12 February 2004 (12.02.2004)
Name and mailing adress of the ISA/AT Austrian Patent Office Dresdner Straße 87, A-1200 Vienna Facsimile No. 1/53424/535	Authorized officer SLABY S. Telephone No. 1/53424/348

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/IN 03/00177-0

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
A		none	
WO A 241919		none	